REMARKS

The issues outstanding in the Office Action mailed October 15, 2008, are the rejections under 35 U.S.C. 112 first and second paragraphs. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Rejections Under 35 U.S.C. 112, First Paragraph

Claims 1-11, 13-15 and 17-19 have been rejected under 35 U.S.C. 112, first paragraph. It is argued, at pages 2 and 3 of the Office Action, that these claims are non-enabled to the extent that they recite derivatives, solvates or stereoisomers of the claimed compounds. While Applicants respectfully disagree with this analysis, for the reasons of record, these terms have been eliminated from claim 1 ("derivative") and claim 9 ("derivative, solvate, stereoisomer"). Accordingly, it is submitted that this issue is moot, and withdrawal of the rejection is respectfully requested.

Claims 14 and 15 have been rejected under 35 U.S.C. 112, first paragraph, as it is argued at page 7 of the Office Action that the term "additional medicament active ingredients" is not enabled. Again, while Applicants respectfully disagree for the reasons of record, in order to expedite prosecution this term has also been canceled from the relevant claims. Withdrawal of this rejection is therefore also respectfully requested.

Claims 17 and 19 have been rejected under 35 U.S.C. 112, first paragraph, as it is argued at page 10 of the Office Action that the specification does not enable treating the specific diseases recited in these claims. Applicants respectfully disagree with this analysis.

At page 10 of the Office Action, it is apparently argued that it is necessary to assess whether the compounds agonize or antagonize the 5-HT_1A receptors. The Office Action argues that there are no assays describing the 5-HT receptors in the specification. It is first respectfully submitted that nowhere does the present specification state that such measurement is essential to employing the therapeutic methods of claims 17 and 19. In fact, the present application discusses how to determine bioavailability of the compounds of the invention (see page 16, line 10 to page 18, line 32) and provides in vivo bioavailability values. See figure 2, for example. In addition,

one of ordinary skill in the art would, as of the time of filing the present application, know without question how to assess agonism or antagonism to these receptors for the present compounds, using only routine experimental methods. In particular, one of ordinary skill in the art would know that agonism and antagonism at the 5-HT_{1d} receptor can be assessed measuring labeled 5-HT release from guinea pig cortical slices as described by Matzen et al. (Matzen et al., J Med Chem 43, 1149, 2000). As for 5-$HT_{1A,}$ 5-$HT_{2A}$and 5-HT_{2C} receptors, agonistic as well as antagonistic activity can be determined using GTPgammaS binding method. This method is carried out as described in Heinrich et al. (Heinrich et al., Biorg Med Chem 12, 4843, 2004), Bartoszyk et al. (Bartoszyk et al., Eur J Pharmacol 473, 229, 2003) and Pullar et al. (Pullar et al., Eur J Pharmacol 432, 9, 2001).

In accordance with the above-noted methods, as further evidence of the activity of the present compounds, and the ability of one of ordinary skill in the art used well known methods to determine their agonistic or antagonistic activity, Applicants call attention to the attached Declaration Under 37 C.F.R. 1.132 where such activity for compounds of the invention has been measured. Thus, this basis for rejection clearly does not stand.

In addition, it appears that, at page 10 of the Office Action, it is argued that there is no art recognized correlation between the activities of the present compounds binding to 5-HT_{1A} receptors and treatment of the diseases in claims 17 and 19. Applicants also respectfully disagree with this analysis. It is submitted to be well known that compounds having such activities can be used as antidepressants as substantiated in the following discussed articles. It is first noted that selective serotonin uptake inhibitors(SSRIs) are known to be safe and effective compounds for the treatment of depression in clinical settings. Studies have shown that the acute administration of SSRIs such as citalopram and fluoxetine increases extracellular 5-HT levels in the brain to a greater or lesser extent, dependent on the brain region studied and on particular doses used (reviewed by (Fuller, 1994)). This enhancement of serotonergic transmission is believed to be at least one reason for the therapeutic effects of the SSRIs in depression. Clinically, a latency of about 3 – 4 weeks of treatment is observed for the SSRIs to develop a full antidepressant effect. This is explained by the elevation of 5-HT in the midbrain raphe nucleus region, followed by an activation of somatodendritic 5-HT_{1A} autoreceptors and a subsequent reduction of terminal

synaptic 5-HT release in those parts of the forebrain receiving serotonergic projections from the dorsal (e.g. striatum and frontal cortex) and median (e.g. hippocampus) raphe nuclei. After several weeks of SSRI treatment, the 5-HT_{1A} autoreceptors desensitize, resulting in an increase in serotonergic transmission. In support, preclinical studies utilizing microdialysis have demonstrated that co-administration of a 5-HT_{1A} antagonists (e.g. WAY100907; (Romero, Hervas et al., 1996)) or the mixed 5-HT1A/ß antagonist pindolol (Dreshfield, Wong et al., 1996), (Hjorth and Auerback, 1996) potentiates the acute effects of SSRIs on extracellular 5-HT levels. Consequently, in clinical trials the combination of SSRIs with pindolol has been shown to enhance the onset of antidepressant action ((Xanardi, Artigas et al., 1997), (Bordet, Thomas et al., 1998), (Groenink, Derion et al., 1995). Thus, the chromenonindol derivatives of the present invention, 5-HT_{1A} agonists, are able to enhance 5-HT levels in the rat frontal cortex in vivo, and are efficacious in the treatment of depression.

Moreover, the compounds of the invention can further be used for the treatment of other neurological diseases as claimed and substantiated by below listed non-patent documents:

1) **Brown AD et al. (2007) Designing drugs for the treatment of female sexual dysfunction. Drug Discov Today 12: 757-66:**
   teaches that clinical data involving drugs affecting serotonin indicates utility in treating dysfunction of female sexual desire, arousal, or orgasm.
2) **De Angelis L (2002) 5.HT2A antagonists in psychiatric disorders. Curr Opin Invest Drugs 3: 106-12:**
   Several lines of evidence support a role for serotoninergic (5-HT) system abnormalities in the pathogenesis and treatment of several psychiatric disorders. This review summarizes information about the association between the 5-HT2A receptor gene and its relevance to schizophrenia, tardive dyskinesia, major depression, suicidality, anorexia nervosa and obsessive-compulsive disorder. Additionally, findings are reviewed on the importance of 5-HT2A receptor antagonism in contributing to the therapeutic effect of several clinically effective and potential atypical antipsychotics as well as several antidepressants. In conclusion, the ability of selective 5-HT2A receptor antagonists to interfere with the heightened state of dopamine activity without altering basal tone, shows that these drugs

possessantipsychotic activity and provides the basis for new therapies for psychosis and drug dependence.

3) **Di Giovanni G et al. (2006) Serotonin involvement in the basal ganglia pathophysiology: could the 5-HT2C receptor be a new target for thereapeutic stragegies? Curr Med Chem 13: 3069-81;**

The basal ganglia are a highly interconnected group of subcortical nuclei in the vertebrate brain that play a critical role not only in the control of movements but also in some cognitive and behavioural functions. Several recent studies have emphasized that serotonergic pathways in the central nervous system (CNS) are intimately involved in the modulation of the basal ganglia and in the pathophysiology of human involuntary movement disorders. These observations are supported by anatomical evidence demonstrating large serotonergic innervation of the basal ganglia. In fact, serotonergic terminals have been reported to make synaptic contacts with dopamine (DA)-containing neurons and gamma-aminobutyric acid (GABA)-containing neurons in the striatum, globus pallidus, subthalamus and substantia nigra. In addition, the involvement of 5-HT2C receptors in neurological disorders such as Parkinson's disease and other related motor disorders, and their management with drugs blocking the 5-HT2C receptor is discussed.

4) **Goddard AW et al. (2008) Serotonergic mechanism in the treatment of obseesive-compulsive disorder. Drug Discov Today 13: 325-32:**

Obsessive-compulsize disorder (OCD) is a disabling psychiatric condition affecting 1-2% of the community. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the drug treatments of choice for OCD.

5) **Guiliano F, Hellstrom WJ (2008) The pharmacological treatment of premature ejaculation. BJU Int 102: 668-75:**

6) **Kiton SL (2007) 5-Hydroxytryptamine (5-HT) receptor ligands. Curr Pharm Des 13: 2621-37:**

Serotonin (5-HT) receptors are part of the G protein-coupled and igand-gated ion channel

families. 5-HT receptors are part of the G protein-coupled and ligand-gated ion channel families. 5-HT exerts its diverse actions by binding to cell surface receptors which can be classified into seven distinct families (5-HT1 to 5-HT7) according to their structural diversity and mode of action. Some of the 5-HT families are comprised of multiple receptors which share similar structural and mechanistic properties but display very different operational profiles. Evidence continues to mount in support of the important roles of the 5-HT receptors in various neuropsychiatric disorders such as anxiety, depression, schizophrenia, migraine and drug addiction. A number of selective/non-selective 5-HT agonist and antagonist ligands (drugs) have been developed to challenge many of these disease states.

7) **Lacivita E et al. (2008) 5-HT1A receptor, an old target for new therapeutic agents. Curr Top Med Chem 8: 1024-34;**

The serotonin receptor subtype 5 HT(1A) was one of the first serotonin receptor subtypes pharmacologically characterized. Over the last twenty years the 5 HT (1A) receptor has been the object of intense research efforts as witnessed by the 5 HT(1A) acting drugs marketed as anxiolytics. In recent years, several new chemical entities targeting the 5 HT(1A) receptor (alone or in combination with other molecular targets) have been proposed for novel therapeutic indications (neuroprotection, cognitive impairment, Parkinson Disease and related disorders, pain treatment).

8) **Lutsep HL (2005) Repinotan, a 5-HT1A agonist, in the treatment of acute ischemic stroke, Curr Drug Targets CNS Neurol Disord 4: 119-20:**

Serotonin agonists can reduce glutamate-induced excitotoxicity in cerebral ischemia. The potent 5-HT1A agonist BAY x 3702, or repinotan, has reduced cortical infarct volume in pre-clinical models even when given 5 hours after injury. Early clinical trials showed that the drug was safe, and displayed primarily serotonergic side effects such s nausea and vomiting. A phase llb trail in moderate to moderately severe strokes completed enrolment in June 2004,

9) **Nance PW (2001) Alpha adrenergic and serotonergic agents in the treatment of**

spastic hypertonia. Phys Med Rehabil Clin N Am 12: 889-905:

10) **Sandyk R (2008) Serotonergic mechanisms in amyotrophic lateral sclerosis. Int J Neurosci 116: 775-826:**

Serotonin (5-HT) has been intimately linked with global regulation of motor behaviour, local control of motoneuron excitability, functional recovery of spinal motoneurons as well as neuronal maturation and aging. Selective degeneration of motoneurons is the pathological hallmark of amyotrophic lateral sclerosis (ALS). Motoneurons that are preferentially affected in ALS are also densely innervated by 5-HT neurons (e.g., trigeminal, facial, ambituus, and hypoglossal brainstem nuclei as well as ventral horn and motor cortex.

11) **Sanger DJ et al., (2007) New perspectives for the treatment of disorder of sleep and arousal. Ann Pharm Fr 65: 268-74.**

12) **Steffen KJ et al. (2006) Emerging drugs for eating disorder treatment. Expert Opin Emerg Drugs 11: 315-36:**

Anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) comprise the currently recognized eating disorders. Although distinct diagnostic entities, they share certain forms of comorbid psychopathology, particularly anxiety and mood disorders. BN and BED have been studied most intensively as targets for pharmacotherapy. The list of drugs tested in eating disorders is substantial; however, the number of therapeutic classes of medications tested in these conditions is relatively modest. Antidepressant medications, including tricyclic antidepressants, selective serotonin re-uptake inhibitors, as well as some of the novel antidepressants, have shown evidence of some therapeutic value in both BN and BED.

Accordingly, it is submitted that these references provide evidence that the presently claimed compounds which are serotonin reuptake inhibitors have utility in the methods stated in the claims. Withdrawal of the rejection is therefore respectfully requested.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-11, 13-15 and 17-19 have been rejected under 35 U.S.C. 112, second paragraph. Cancellation of the term "derivative" renders this rejection moot, and withdrawal thereof is respectfully requested.

The claims of the application are submitted to be in condition for allowance. However, should the Examiner have any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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